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(54) Title PHARMACEUTICAL COMPOSITIONS COMPRISING
CYCLOSPORINS

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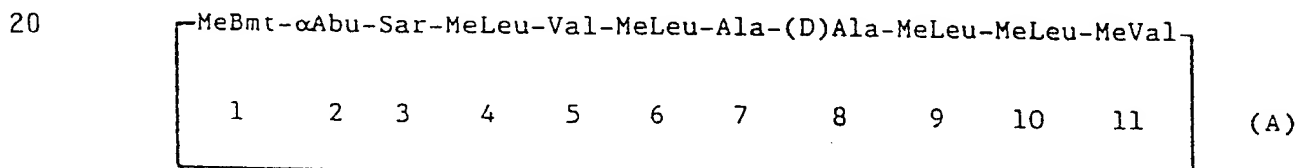
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PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORINS

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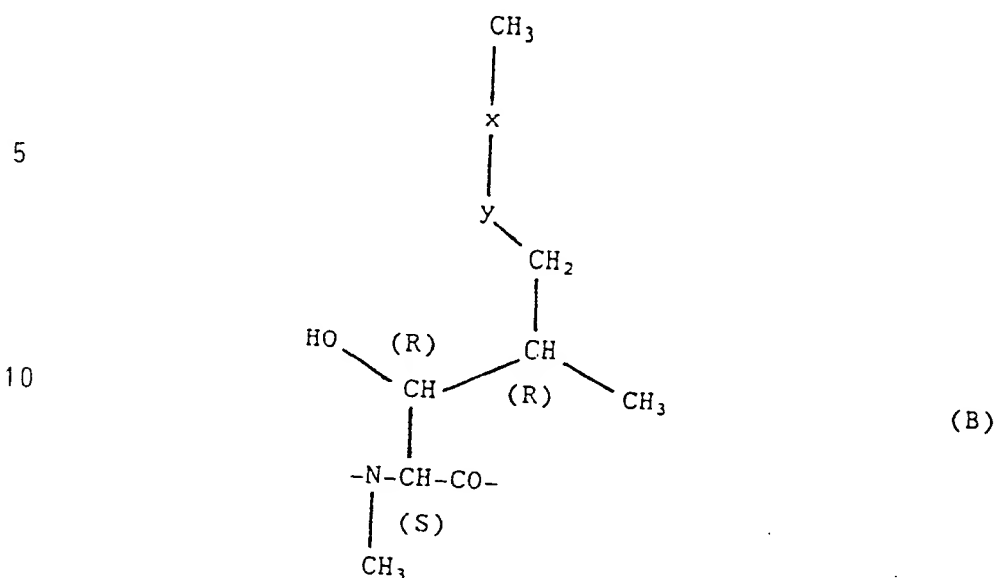
The present invention relates to novel galenic formulations comprising a cyclosporin as active ingredient.

10 The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated endcapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or
15 Cyclosporine, also known as cyclosporin A and commercially available under the Registered Trade Mark SANDIMMUN^R or SANDIMMUNE^R. Ciclosporin is the cyclosporin of formula A.



25 wherein -MeBmt- represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue of formula B

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in which -x-y- is -CH=CH- (trans).

20 As the parent of the class Ciclosporin has so far received the most
 attention. The primary area of clinical investigation for Ciclosporin
 has been as an immunosuppressive agent, in particular in relation to
 its application to recipients of organ transplants, e.g. heart, lung,
 combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and
 corneal transplants and, in particular, allogenic organ transplants.
 25 In this field Ciclosporin has achieved a remarkable success and
 reputation.

30 At the same time, applicability of Ciclosporin to various autoimmune
 diseases and to inflammatory conditions, in particular inflammatory
 conditions with an aetiology including an autoimmune component such as
 arthritis (for example rheumatoid arthritis, arthritis chronica
 progrediente and arthritis deformans) and rheumatic diseases, has been
 intensive and reports and results in vitro, in animal models and in
 clinical trials are wide-spread in the literature. Specific
 35 auto-immune diseases for which Ciclosporin therapy has been proposed
 or applied include, autoimmune hematological disorder (including e.g.

hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Further areas of investigation have been potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis and, yet more recently, use as an agent for reversing or abrogating anti-neoplastic agent resistance in tumours and the like.

Since the original discovery of ciclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, *Helv. Chim. Acta.* 60, 1247-1255 (1977); Traber et al. 2, *Helv. Chim. Acta.* 65 no. 162, 1655-1667 (1982); Kobel et al., *Europ. J. Applied Microbiology and Biotechnology* 14, 273-240 (1982); and von Wartburg et al., *Progress in Allergy*, 38, 28-45 (1986)], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the so called dihydro-cyclosporins [in which the moiety -x-y- of the -MeBmt- residue (Formula B above) is saturated to give -x-y- = -CH₂-CH₂-; derivatised cyclosporins (e.g. in which a further substituent is introduced at the

α -carbon atom of the sarcosyl residue at the 3-position of the cyclosporin molecule); cyclosporins in which the -MeBmt- residue is present in isomeric form (e.g. in which the configuration across positions 6' and 7' of the -MeBmt- residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence, employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger - see e.g. Traber 1, Traber 2 and Kobel loc. cit.; U.S. Patents Nos. 4 108 985, 4 210 581 and 4 220 641; European Patent Publication Nos. 0 034 567 and 0 056 782; International Patent Publication No. WO 86/02080; Wenger 1, Transp. Proc. 15, Suppl. 1:2230 (1983); Wenger 2, Angew. Chem. Int. Ed., 24, 77 (1985); and Wenger 3, Progress in the Chemistry of Organic Natural Products 50, 123 (1986).

The class comprised by the cyclosporins is thus now very large indeed and includes, for example, [Thr]²-, [Val]²-, [Nva]²- and [Nva]²-[Nva]⁵-Ciclosporin (also known as cyclosporins C,D, G and M respectively), [3-O-acyl-MeBmt]¹-Ciclosporin (also known as cyclosporin A acetate), [Dihydro-MeBmt]¹-[Val]²-Ciclosporin (also known as dihydro-cyclosporin D), [(D)Fluoromethyl-Sar]³-Ciclosporin, [(D)Ser]⁸-Ciclosporin, [MeIle]¹¹-Ciclosporin, [(D)MeVal]¹¹-Ciclosporin (also known as cyclosporin H), [MeAla]⁶-Ciclosporin, [(D)Pro]³-Ciclosporin and so on.

[In accordance with now conventional nomenclature for cyclosporins, these are defined by reference to the structure of Ciclosporin (i.e. Cyclosporin A). This is done by first indicating the amino acid residues present which differ from those present in Ciclosporin (e.g. "[(D)Pro]³" to indicate that the cyclosporin in question has a -(D)Pro- rather than -Sar- residue at the 3-position) and then applying the term "Ciclosporin" to characterise remaining residues which are identical to those present in Ciclosporin. Individual residues are numbered starting with the residue -MeBmt- or -dihydroMeBmt- in position 1.]

Very many of these further cyclosporins exhibit comparable

pharmaceutical utility to Ciclosporin or more specific utility, for example activity particularly in reversing tumor resistance to cytostatic therapy, and proposals for their application as therapeutic agents abound in the literature.

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Despite the very major contribution which Ciclosporin has made, in particular to the areas of organ transplant and the therapy of autoimmune diseases, difficulties encountered in providing more effective and convenient means of administration as well as the reported occurrence of undesirable side reactions, in particular nephrotoxic reaction, have been obvious serious impediments to its wider use or application. The cyclosporins are characteristically highly hydrophobic. Proposed liquid formulations, e.g. for oral administration of cyclosporins, have hitherto been based primarily on the use of ethanol and oils or similar excipients as carrier media. Thus the commercially available Ciclosporin drink-solution employs ethanol and olive oil as carrier medium in conjunction with labrafil as a surfactant - see e.g. US patent no. 4,388,307. Use of the drink-solution and similar compositions as proposed in the art is however accompanied by a variety of difficulties.

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First, the necessity to use oils or oil based carriers may lend the preparations an unpleasant taste or otherwise reduce palatability, in particular for the purposes of long-term therapy. These effects can be masked by presentation in gelatin capsule form. However, in order to maintain the cyclosporin in solution, the ethanol content has to be kept high. Evaporation of the ethanol, e.g. from capsules or from other forms, e.g. when opened, results in the development of a cyclosporin precipitate. Where such compositions are presented in e.g. soft gelatin encapsulated form, this particular difficulty necessitates packaging of the encapsulated product in an air-tight compartment, for example an air-tight blister or aluminium-foil blister-package. This in turn renders the product both bulky and more expensive to produce. The storage characteristics of formulations as aforesaid are far from ideal.

Bioavailability levels achieved using existing oral cyclosporin dosage systems are also low and exhibit wide variation between individuals, individual patient types and even for single individuals at different times during the course of therapy. Thus reports in the literature indicate that currently available therapy employing the commercially available Ciclosporin drink solution provides an average absolute bioavailability of ca. 30% only, with marked variation between individual groups, e.g. between liver (relatively low bioavailability) and bone-marrow (relatively high bioavailability) transplant recipients. Reported variation in bioavailability between subjects has varied from anything between one or a few percent for some patients to as much as 90% or more for others. And as already noted, marked change in bioavailability for individuals with time is frequently observed.

To achieve effective immunosuppressive therapy, cyclosporin blood or blood serum levels have to be maintained within in a specified range. The required range can in turn vary, depending on the particular condition being treated, e.g. whether therapy is to prevent transplant rejection or for the control of an autoimmune disease, and on whether or not alternative immunosuppressive therapy is employed concomitantly with cyclosporin therapy. Because of the wide variations in bioavailability levels achieved with conventional dosage forms, daily dosages needed to achieve required blood serum levels will also vary considerably from individual to individual and even for a single individual. For this reason it is necessary to monitor blood/blood-serum levels of patients receiving cyclosporin therapy at regular and frequent intervals. Monitoring of blood/blood-serum levels, which is generally performed by RIA or equivalent immunoassay technique, e.g. employing monoclonal antibody based technology, has to be carried out on a regular basis. This is inevitably time consuming and inconvenient and adds substantially to the overall cost of therapy.

Beyond all these very evident practical difficulties lies the occurrence of undesirable side reactions already alluded to, observed employing available oral dosage forms.

Several proposals to meet these various problems have been suggested in the art, including both solid and liquid oral dosage forms. An overriding difficulty which has however remained is the inherent insolubility of the cyclosporins, e.g. Ciclosporin, in aqueous media and hence provision of a dosage form which can contain cyclosporins in sufficiently high concentration to permit convenient use and yet meet the required criteria in terms of bioavailability, e.g. enabling effective resorption from the stomach or gut lumen and achievement of consistent and appropriately high blood/blood-serum levels.

The particular difficulties encountered in relation to oral dosaging with cyclosporins have inevitably led to restrictions in the use of cyclosporin therapy for the treatment of relatively less severe or endangering disease conditions. A particular area of difficulty in this respect has been the adoption of cyclosporin therapy in the treatment of autoimmune diseases and other conditions affecting the skin, for example for the treatment of atopic dermatitis and psoriasis and, as also widely proposed in the art, for hair growth stimulation, e.g. in the treatment of alopecia due to ageing or disease.

Thus while oral Ciclosporin therapy has shown that the drug is of considerable potential benefit to patients suffering e.g. from psoriasis, the risk of side-reaction following oral therapy has prevented common use. Various proposals have been made in the art for application of cyclosporins, e.g. Ciclosporin, in topical form and a number of topical delivery systems have been described. Attempts at topical application have however failed to provide any demonstrably effective therapy. A means of topical application providing effective dermal delivery and useful, e.g. for the treatment of psoriasis, would effectively make cyclosporin therapy available to, what is, a major patient population at need.

By the present invention there are provided novel cyclosporin galenic formulations in the form of a micro-emulsion pre-concentrate and/or based on the use of particular solvent media as hereinafter defined,

which meet or substantially reduce difficulties in cyclosporin, e.g. Ciclosporin, therapy hitherto encountered in the art. In particular it has been found that the compositions of the invention permit the preparation of solid, semi-solid and liquid compositions containing a cyclosporin in sufficiently high concentration to permit, e.g. convenient oral administration, while at the same time achieving improved efficacy, e.g. in terms of bioavailability characteristics.

More particularly it has been found that compositions in accordance with the present invention enable effective cyclosporin dosaging with concomitant enhancement of resorption/bioavailability levels, as well as reduced variability in resorption/bioavailability levels achieved both for individual patients receiving cyclosporin therapy as well as between individuals. By application of the teachings of the present invention cyclosporin dosage forms are obtainable providing reduced variability in achieved cyclosporin blood/blood serum levels between dosages for individual patients as well as between individuals/individual patient groups. The invention thus enables reduction of cyclosporin dosage levels required to achieve effective therapy. In addition it permits closer standardisation as well as optimisation of on-going daily dosage requirements for individual subjects receiving cyclosporin therapy as well as for groups of patients undergoing equivalent therapy.

By closer standardisation of individual patient dosaging rate and blood/blood-serum level response, as well as dosaging and response parameters for patient groups, monitoring requirements may be reduced, thus substantially reducing the cost of therapy.

By reduction of required cyclosporin dosaging/standardisation of achieved bio-availability characteristics, the present invention also offers a means permitting reduction in the occurrence of undesirable side-effects, in particular nephrotoxic reaction, in patients undergoing cyclosporin therapy.

In addition, the present invention enables the preparation of compositions which are non-alkanol based, e.g. which may be free or

substantially free of ethanol. Such compositions avoid stability and related processing difficulties as hereinbefore discussed, inherent to known alkanolic compositions. The invention thus provides inter al. compositions which are better adapted, e.g. for presentation in capsule, e.g. hard or soft gelatin capsule form and/or which eliminate or substantially reduce packaging difficulties, for example as hereinbefore discussed, e.g. for soft gelatin encapsulated forms.

In relation to topical application, the present invention further enables the preparation of novel galenical formulations comprising a cyclosporin, e.g. Ciclosporin, as active ingredient and permitting improved treatment for autoimmune diseases affecting the skin, in particular, of dermatological disease involving morbid proliferation and/or keratinisation of the epidermis, especially of psoriasis and atopic dermatosis. Topically applicable compositions in accordance with the invention are also of use in the treatment of alopecia, e.g. for use in the promotion of hair growth.

In a first aspect, the present invention specifically provides pharmaceutical compositions comprising a cyclosporin as active ingredient, which compositions are in the form of an "oil-in-water microemulsion pre-concentrate".

By the term "oil-in-water microemulsion pre-concentrate" as used herein is meant a system capable on contacting with, e.g. addition to, water of providing an oil-in-water microemulsion. The term microemulsion as used herein is used in its conventionally accepted sense as a non-opaque or substantially non-opaque colloidal dispersion comprising water and organic components including hydrophobic (lipophilic) organic components. Microemulsions are identifiable as possessing one or more of the following characteristics. They are formed spontaneously or substantially spontaneously when their components are brought into contact, that is without substantial energy supply, e.g. in the absence of heating or the use of high shear equipment or other substantial agitation. They exhibit thermodynamic stability. They are monophasic. They are substantially non-opaque,

i.e. are transparent or opalescent when viewed by optical microscopic means. In their undisturbed state they are optically isotropic, though an anisotropic structure may be observable using e.g. x-ray technique.

Microemulsions comprise a dispersed or particulate (droplet) phase, the particles of which are of a size less than 2,000 Å, hence their optical transparency. The particles of a microemulsion may be spherical, though other structures are feasible, e.g. liquid crystals with lamellar, hexagonal or isotropic symmetries. Generally, microemulsions comprise droplets or particles having a maximum dimension (e.g. diameter) of less than 1,500 Å, e.g. typically from 100 to 1,000 Å.

[For further discussion of the characteristics of microemulsions see, e.g. Rosof, Progress in Surface and Membrane Science, 12, 405 et seq. Academic Press (1975); Friberg, Dispersion Science and Technology, 6 (3), 317 et seq. (1985); and Müller et al. Pharm. Ind., 50 (3), 370 et seq. (1988)].

From the foregoing it will be understood that the "oil-in-water microemulsion pre-concentrates" of the invention are galenic systems comprising a cyclosporin as active ingredient capable of forming an oil-in-water microemulsion, spontaneously or substantially spontaneously on contact with water alone.

Pharmaceutical "oil-in-water microemulsion pre-concentrate" compositions comprising cyclosporins as active ingredient are novel. Accordingly in one aspect the present invention provides:

- A) A pharmaceutical composition comprising a cyclosporin as active ingredient,
1) a hydrophilic phase,
2) a lipophilic phase, and
3) a surfactant,
which composition is an "oil-in-water microemulsion pre-concentrate".

(The term "pharmaceutical composition" as used herein and in the accompanying claims is to be understood as defining compositions of which the individual components or ingredients are themselves pharmaceutically acceptable, e.g. where oral administration is
5 foreseen, acceptable for oral use and, where topical administration is foreseen, topically acceptable.)

The cyclosporin is carried in the lipophilic phase. Suitably both the hydrophilic and lipophilic phases will serve as carrier medium.
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The defined "microemulsion pre-concentrates" of the invention are of a type providing oil-in-water (also o/w) microemulsions. As will be appreciated however, compositions in accordance with (A) may contain minor quantities of water or otherwise exhibit fine structural
15 features characteristic of microemulsions, e.g. of o/w or w/o (water-in-oil) type. The term "oil-in-water microemulsion pre-concentrate" as used herein is accordingly to be understood as embracing such possibilities.

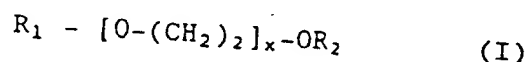
Microemulsions obtained on contacting the "microemulsion pre-concentrate" compositions of the invention with water or other aqueous medium exhibit thermodynamic stability, that is they will remain stable at ambient temperatures, e.g. without clouding or regular emulsion size droplet formation or precipitation, over
20 prolonged periods of time. [It will of course be understood that, to obtain a microemulsion, adequate water will be required. While the upper limit of dilution is not critical, a dilution of 1:1, e.g. 1:5 "p.p.w. ("microemulsion pre-concentrate": H₂O) or more will generally be appropriate.] Preferably, on contacting with water, the
25 "microemulsion pre-concentrate" compositions of the invention are capable of providing microemulsions which remain stable at ambient temperatures, e.g. as evidenced by absence of any optically observable clouding or precipitation, over periods of at least 2 hours, more preferably at least 4 hours, most preferably at least 12 to 24 hours.
30 Microemulsions obtainable from "microemulsion pre-concentrates" of the
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invention, e.g. at dilutions as indicated above, will preferably have an average particle size of less than about 1,500 Å, more preferably of less than about 1,000 or 1,100 Å, e.g. down to about 150 or 200 Å.

5 Especially preferred in accordance with the present invention are compositions as defined under (A) in which the hydrophilic phase comprises:

- 10 1.1. A pharmaceutically acceptable C₁₋₅alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol; or
1.2. 1,2-propyleneglycol.

15 Suitable components (1.1.) are, e.g. di- or partial-, especially partial-, -ethers of mono- or poly-, especially mono- or di-, -oxy-alkanediols comprising from 2 to 12, especially 4 carbon atoms. Preferably the mono- or poly-oxy-alkanediol moiety is straight-chained. Especially suitable for use in accordance with the
20 invention are di- or partial-ethers of formula I



wherein R₁ is C₁₋₅ alkyl or tetrahydrofurfuryl,
25 R₂ is hydrogen, C₁₋₅alkyl or tetrahydrofurfuryl, and
x is an integer of from 1 to 6, especially from 1 to 4, most especially about 2.

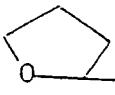
30 Particularly preferred for use in accordance with the invention are partial ethers as defined above, e.g. products of formula I, wherein R₂ is hydrogen.

35 C₁₋₅alkyl moieties in the above defined ethers may be branched or straight chain, e.g. including methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl groups.

Such ethers are known products and commercially available or may be produced analogously to the known products. Especially preferred products of formula I for use in relation to the present invention are those known and commercially available under the trade names Transcutol and Glycofurol.

Transcutol is the compound diethyleneglycol monoethyl ether of formula I, wherein $R_1 = C_2H_5$, $R_2 = H$ and $x = 2$.

Glycofurol, also known as tetrahydrofurfuryl alcohol polyethylene glycol ether or α -(tetrahydrofuranyl)- ω -hydroxypoly(oxy-1,2-ethanediyl) has the

formula I wherein $R_1 =$  $, R_2 = H$ and x has an average value of from 1 to 2. It has an average molecular weight of ca. 190; a b.p. of from ca. 80-100°C (at 40N/m²), a density of ca. 1.070 - 1.090 g/cm³ (at 20°C); a hydroxy value of ca. 300-400; a refractive index of ca. 1.4545 (sodium D line, 589mm) (at 40°C); and a viscosity of ca. 8-18 mN s/m² (at 20°). [c.f. "Handbook of Pharmaceutical Excipients, published by American Pharmaceutical Association/ The Pharmaceutical Society of Great Britain (1986), p. 127 and Fiedler, "Lexikon der Hilfstoffe", 3rd edition (1989), p. 577.]

The precise properties of Glycofurol vary according to relative purity. Thus lower quality grades contain significant amounts of tetrahydrofurfuryl alcohol and other impurities. For the purposes of the present invention Glycofurol 75, designating a product meeting the above physical data and for which the fraction having the formula I above in which $x = 1-2$ amounts to a minimum of 95%, is preferred.

Use of components defined under (1.1.) and (1.2.) above has in particular been found to provide compositions in accordance with (A) in which the hydrophilic phase is especially well suited as cyclosporin carrier medium, e.g. in which the hydrophilic phase enables cyclosporin-loading of the composition, adequate for convenient therapeutic dosaging, e.g. for oral administration.

Compositions in accordance with (A) comprising components as defined under (1.1.) and/or (1.2.) as hydrophilic phase may of course additionally include one or more further ingredients as hydrophilic phase component. Preferably however any additional components will comprise materials in which the cyclosporin active ingredient is sufficiently soluble, such that the efficacy of the hydrophilic phase as cyclosporin carrier medium is not materially impaired. Examples of possible additional hydrophilic phase components are lower (e.g. C₁₋₅) alkanols, in particular ethanol.

While, however, use of alkanols, e.g. ethanol, as hydrophilic phase component is contemplated by the present invention, for reasons hereinbefore discussed, this will be generally less preferred. Preferably, compositions as defined under (A) will be non-alkanol-based, i.e. will not comprise an alkanol as a predominant hydrophilic phase component. Suitably the hydrophilic phase comprises less than 50%, more preferably less than 25%, most preferably less than 10% by weight alkanolic components. Most suitably, the hydrophilic phase will be free or substantially free of alkanolic components, i.e. comprise less than 5%, preferably less than 2%, e.g. from 0 to 1% alkanolic components. By "alkanol" is meant, in particular, C₁₋₅ alkanols, especially ethanol.

In an especially preferred embodiment the hydrophilic phase of compositions defined under (A) will consist or consist essentially of components as defined under (1.1.) or (1.2.) above, in particular Transcutol, Glycofurol and/or 1,2-propylene glycol. Most suitably they will consist or consist essentially of either components (1.1.) or component (1.2.).

Compositions in accordance with (A) comprising a component (1.1), especially Glycofurol, are of particular interest in that they are well adapted for presentation in soft gelatin encapsulated form. Such compositions have, in accordance with the invention, also been found to exhibit surprisingly advantageous stability, e.g. as evidenced in long-term stability tests at normal and elevated temperatures. Such

compositions are thus particularly well suited to meet difficulties commonly encountered in transport and storage of drug products, including long term storage at the user end, e.g. in hospitals, clinics and like facilities.

5 Compositions defined under (A) additionally comprise a lipophilic phase (2).

10 Suitable components for use as lipophilic phase include any pharmaceutically acceptable solvent which is non-miscible with the selected hydrophilic phase, e.g. as defined under (1.1.) or (1.2.). Such solvents will appropriately be devoid or substantially devoid of surfactant function. Especially suitable components for use as lipophilic phase components (2) are, e.g.:

15 Fatty acid triglycerides, preferably medium chain fatty acid triglycerides. Especially suitable are neutral oils, e.g. neutral plant oils, in particular fractionated coconut oils such as known and commercially available under the trade name Miglyol (c.f. Fiedler, 20 loc. cit. pp. 808-809), including the products:

Miglyol 810: a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight : ca. 520. Fatty acid composition = C₆ max. 2%, C₈ ca. 65-75%, C₁₀ ca. 25-35%, C₁₂ max. 2%; acid no. = ca. 0.1; saponification no. = ca. 340-360; iodine no. = max. 1;

25 Miglyol 812: a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight = ca. 520. Fatty acid composition = C₆ max. ca. 3%, C₈ ca. 50-65%, C₁₀ ca. 30-45%, C₁₂ max. 5%; acid no. = ca. 0.1; saponification no. = ca. 330-345; iodine no. = max. 1;

30 Miglyol 818: a caprylic-capric-linoleic acid triglyceride having a molecular weight = ca. 510. Fatty acid composition = C₆ max. 3, C₈ ca. 45-60, C₁₀ ca. 25-40, C₁₂ ca. 2-5, C_{18:2} ca. 4-6; acid no. = max. 0.2;

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saponification no. = ca. 315-335, iodine no. = max. 10; and

Captex 355⁽¹⁾ a caprylic-capric acid triglyceride. Fatty acid content = caproic ca. 2%, caprylic ca. 55%, capric ca. 42%. Acid no. = max. 0.1; saponification no. = ca. 325-340; iodine no. = max. 0.5.

Also suitable are caprylic-capric acid triglycerides such as known and commercially available under the trade name Myritol (c.f. Fiedler loc. cit., p. 834) including the product Myritol 813 which has an acid no. = max. 1, a saponification no. = ca. 340-350 and an iodine no. = ca. 0.5.

Further suitable products of this class are Capmul MCT⁽¹⁾, Captex 300⁽¹⁾ and Captex 800⁽¹⁾, Neobee M5⁽²⁾ and Mazol 1400⁽³⁾.

[(1) = Capital City Products, P.O. Box 569, Columbus, OH, USA. (2) = Stepan, PVO Dept., 100 West Hunter Ave., Maywood, NJ 07607, USA. (3) = Mazer Chemicals, 3938 Porett Drive, Gurnee, IL, USA).]

Especially preferred as lipophilic phase component is the product Miglyol 812.

Compositions in accordance with the invention defined under (A) further comprise a pharmaceutically acceptable surfactant (3). The surfactant component may comprise (3.1.) hydrophilic or (3.2.) lipophilic surfactants, or mixtures thereof. Especially preferred are non-ionic hydrophilic and non-ionic lipophilic surfactants. Examples of suitable hydrophilic surfactants for use as surfactant components are e.g.:

3.1.1. Reaction products of natural or hydrogenated vegetable oils and ethylene glycol, i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene

- oxide, e.g. in a molar ratio of from about 1:35 to about 1:60, with optional removal of free polyethyleneglycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable are the various tensides available under the trade name Cremophor. Particularly suitable are the products Cremophor RH 40 having a saponification no. ca. 50-60, an acid no. = <1, an iodine no. = <1, a water content (Fischer) = <2%, an n_D^{60} = ca. 1,453 - 1,457 and an HLB = ca. 14 - 16; Cremophor RH 60 having a saponification no. = ca. 40 - 50, an acid No. = <1, an iodine no. = <1, a water content (Fischer) = ca. 4.5-5.5%, an n_D^{25} = ca. 1.453 - 1,457 and an HLB = ca. 15 - 17; and Cremophor EL having a molecular weight (by steam osmometry) = ca. 1630, a saponification no. = ca. 65-70, an acid no. = ca. 2, an iodine no. = ca. 28 - 32 and an n_D^{25} = ca. 1.471 (c.f. Fiedler loc. cit. pp. 326-327). Also suitable for use in this category are the various tensides available under the trade name Nikkol, e.g. Nikkol HCO-60. The said product Nikkol HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: Acid no. = ca. 0.3; Saponification no. = ca. 47.4; Hydroxy value = ca. 42.5; pH (5%) = ca. 4.6; Color APHA = ca. 40; m.p. = ca. 36.0°C; Freezing point = ca. 32.4°C; H₂O content (% KF) = ca. 0.03;
- 25 3.1.2. Polyoxyethylene-sorbitan-fatty acid esters e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters e.g. of the type known and commercially available under the trade name Tween (c.f. Fiedler, loc. cit. pp. 1300-1304) including the products Tween
- 30 20 [polyoxyethylene(20)sorbitanmonolaurate],
40 [polyoxyethylene(20)sorbitanmonopalmitate],
60 [polyoxyethylene(20)sorbitanmonostearate],
80 [polyoxyethylene(20)sorbitanmonooleate],
65 [polyoxyethylene(20)sorbitantristearate],
35 85 [polyoxyethylene(20)sorbitantrioleate],
21 [polyoxyethylene(4)sorbitanmonolaurate],

61 [polyoxyethylene(4)sorbitanmonostearate], and
81 [polyoxyethylene(5)sorbitanmonooleate].

5 Especially preferred products of this class for use in the
compositions of the invention are the above products Tween 40
and Tween 80;

10 3.1.3. Polyoxyethylene fatty acid esters, for example polyoxyethylene
stearic acid esters of the type known and commercially
available under the trade name Myrj (c.f. Fiedler, loc. cit.,
p. 834) as well as polyoxyethylene fatty acid esters known and
commercially available under the trade name Cetiol HE. (c.f.
15 Fiedler, loc. cit., p. 284); an especially preferred product of
this class for use in the compositions of the invention is the
product Myrj 52 having a $D^{25} = \text{ca. } 1.1.$, m.p. = ca. 40-44°C, an
HLB = ca. 16.9., an acid no. = ca. 0-1 and a saponification no.
= ca. 25-35;

20 3.1.4. Polyoxyethylene-polyoxypropylene co-polymers, e.g. of the type
known and commercially available under the trade names Pluronic
and Emkalyx (c.f. Fiedler, loc. cit., pp. 956-958). An
especially preferred product of this class for use in the
compositions of the invention is the product Pluronic F68;

25 3.1.5. Polyoxyethylene-polyoxypropylene block co-polymers, e.g. of the
type known and commercially available under the trade name
Poloxamer (c.f. Fiedler, loc. cit., pp. 959). An especially
suitable product of this class for use in the compositions of
30 the invention is the product Poloxamer 188;

3.1.6. Dioctylsuccinate, dioctylsodiumsulfosuccinate,
di-[2-ethylhexyl]-succinate or sodium lauryl sulfate;

35 3.1.7. Phospholipids, in particular lecithins (c.f. Fiedler, loc.
cit., pp. 731-733). Lecithins suitable for use in the
compositions of the invention include, in particular, soya bean

lecithins;

5 3.1.8. Propylene glycol mono- and di-fatty acid esters such as
propylene glycol dicaprylate, propylene glycol dilaurate,
propylene glycol hydroxystearate, propylene glycol isostearate,
propylene glycol laurate, propylene glycol ricinoleate,
propylene glycol stearate and so forth (c.f. Fiedler, loc.
cit., pp. 1013 et seq.). Especially preferred is propylene
10 glycol caprylic-capric acid diester as known and commercially
available under the trade name Miglyol 840 (c.f. Fiedler, loc.
cit., p. 809). Miglyol 840 has a fatty acid content = C₆ max.
ca. 3%, C₈ ca. 65-80%, C₁₀ ca. 15-30%, C₁₂ max. 3%. Acid no. =
max. 0.1, iodine no. = ca. 320-340, iodine no. = max. 1; and

15 3.1.9. Bile salts, e.g. alkali metal salts, for example sodium
taurocholate.

Examples of suitable lipophilic surfactants for use as surfactant
component are, e.g.:

20
3.2.1. Trans-esterification products of natural vegetable oil
triglycerides and polyalkylene polyols. Such
trans-esterification products are known from the art and may be
25 obtained e.g. in accordance with the general procedures
described in US Patent No. 3,288,824. They include
transesterification products of various natural (e.g.
non-hydrogenated) vegetable oils for example, maize oil, kernel
oil, almond oil, ground nut oil, olive oil and palm oil and
30 mixtures thereof with polyethylene glycols, in particular
polyethylene glycols having an average molecular weight of from
200 to 800. Preferred are products obtained by
trans-esterification of 2 molar parts of a natural vegetable
oil triglyceride with one molar part of polyethylene glycol
35 (e.g. having an average molecular weight of from 200 to 800).
Various forms of trans-esterification product of the class

defined are known and commercially available under the trade name Labrafil [see Fiedler, loc. cit., 707]. Especially useful as components of the compositions of the invention are the products: Labrafil M 1944 CS, a trans-esterification product of kernel oil and polyethylene glycol having an acid no. = ca. 2, a saponification no. ca. 145 - 175 and an iodine no. = ca. 60 - 90; and Labrafil M 2130 CS, a trans-esterification product of a C₁₂- to C₁₈- glyceride and polyethylene glycol having a melting point = ca. 35 - 40°C., an acid no. = <2, a saponification no. = ca. 185 - 200 and an iodine no. = <3;

3.2.2. Mono-, di- and mono/di-glycerides, especially esterification products of caprylic or capric acid with glycerol. Preferred products of this class are e.g. those comprising or consisting mainly or essentially of caprylic/capric acid mono- and di-glycerides such as are commercially available under the trade name Imwitor (c.f. loc. cit., pp. 645). A particularly suitable product of this class for use in the compositions of the invention is the product Imwitor 742, which is the esterification product of a mixture of ca. 60 p.p.w. caprylic acid and ca. 40 p.p.w. capric acid with glycerol. Imwitor 742 is typically a yellowish crystalline mass, liquid at ca. 26°C; acid no. = max. 2; iodine no. = max. 1; saponification no. = ca. 235 - 275; % monoglycerides = ca. 40-50%; free glycerol = max. 2%; m.p. = ca. 24 - 26°C; unsaponifiables = 0.3% max.; peroxide no. = max. 1;

3.2.3. Sorbitan fatty acid esters e.g. of the type known and commercially available under the trade name Span, for example including sorbitan-monolauryl, -monopalmityl, -monostearyl, -tristearyl, -monooleyl and -trioleylesters - (c.f. Fiedler, loc. cit., pp. 1139-1140);

3.2.4. Pentaerythritol fatty acid esters and polyalkylene glycol ethers, for example pentaerythrite- -dioleate, -distearate, -monolaurate, -polyglycol ether and -monostearate as well as

pentaerythrite-fatty acid esters (c.f. Fiedler, loc. cit. pp. 923-924);

5 3.2.5. Monoglycerides, e.g. glycerol monooleate, glycerol monopalmitate and glycerol monostearate, for example as known and commercially available under the trade names Myvatex, Myvaplex and Myverol (c.f. Fiedler, loc. cit., pp. 836), and acetylated, e.g. mono-and di-acetylated monoglycerides, for example as known and commercially available under the trade name Myvacet (c.f. 10 Fiedler, loc. cit., pp. 835);

3.2.6. Glycerol triacetate or (1,2,3)-triacetin (c.f. Fiedler, loc. cit., pp. 952); and

15 3.2.7. Sterols and derivatives thereof, for example cholesterol and derivatives thereof, in particular phytosterols, e.g. products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof, such as known under the trade name Generol (c.f. 20 Fiedler loc. cit., p.p. 554 and 555) in particular the products Generol 122, 122 E5, 122 E10, and 122 E25.

25 Compositions as defined under (A) above include systems comprising either a single surfactant or mixture of surfactants, e.g. comprising a first surfactant and one or more co-surfactants. Surfactant and co-surfactant combinations may be selected, e.g. from any of the surfactant types indicated under (3.1.1.) to (3.2.7.) above.

30 When the hydrophilic phase comprises a di- or partial-ether as defined under (1.1) above, in particular Transcutol or Glycofurol, use of a single surfactant will generally be sufficient, though co-surfactants may be added if desired, e.g. to further improve stability characteristics. When 1,2-propylene glycol is employed as sole or principle hydrophilic phase component, the use of at least two 35 surfactants, i.e. a surfactant and co-surfactant, will generally be required. Compositions as defined under (A) comprising 1,2-propylene

glycol as hydrophilic phase thus suitably comprise both a surfactant and a co-surfactant.

5 Surfactants as defined under (3.1.1.), (3.1.3.), (3.1.7), (3.2.2.) and (3.2.5.) above are of particular interest for use in compositions as defined under (A). Especially suitable surfactant/co-surfactant combinations are hydrophilic/lipophilic surfactant combinations, e.g. combinations of surfactants in accordance with (3.1.1.) with surfactants in accordance with (3.2.5.).

10 When the surfactant comprises an effective solvent for the cyclosporin active ingredient, as in the case e.g. of surfactants or mixtures of surfactants under (3.1.1.) to (3.2.7.) above, it may be incorporated into compositions as defined under (A), not only as surfactant, but in excess as an additional carrier or co-solvent phase, i.e. as part of the hydrophilic or lipophilic phase.

15 Compositions in accordance with (A) above may also comprise:

20 4. A thickening agent.

Suitable thickening agents may be of those known and employed in the art, including, e.g. pharmaceutically acceptable polymeric materials and inorganic thickening agents, for example of the following types:

25 4.1. Polyacrylate and polyacrylate co-polymer resins, for example poly-acrylic acid and poly-acrylic acid/methacrylic acid resins, such as known and commercially available under the trade name Carbopol (c.f. Fiedler, loc. cit., pp. 254-256), in particular the products Carbopol 934, 940 and 941, and Eudragit (c.f. Fiedler, loc. cit., pp. 486-487), in particular the products Eudragit E, L, S, RL and RS and, most especially, the products Eudragit E, L and S;

30 4.2. Celluloses and cellulose derivatives including: alkyl cellulosides, e.g. methyl-, ethyl- and propyl-celluloses;

hydroxypropyl-celluloses, e.g. hydroxyalkyl-celluloses and hydroxypropylalkyl-celluloses such as hydroxypropyl-methyl-celluloses; acylated celluloses, e.g. cellulose-acetates, cellulose-acetatephthallates, cellulose-acetatesuccinates and hydroxypropylmethyl-cellulose phthallates; and salts thereof such as sodium-carboxymethyl-celluloses. Examples of such products suitable for use in accordance with the present invention are those known and commercially available, e.g. under the trade names Klucel and Methocel (c.f. Fiedler, loc. cit., pp. 688 and 790), in particular the products Klucel LF, MF, GF and HF and Methocel K 100, K 15M, K 100M, E 5M, E 15, E 15M and E 100M;

4.3. Polyvinylpyrrolidones, including for example poly-N-vinylpyrrolidones and vinylpyrrolidone co-polymers such as vinylpyrrolidone-vinylacetate co-polymers. Examples of such compounds suitable for use in accordance with the present invention are those known and commercially available, e.g. under the trade name Kollidon (or, in the USA, Povidone) (c.f. Fiedler, loc. cit., pp. 694-696), in particular the products Kollidon 30 and 90;

4.4. Polyvinyl resins, e.g. including polyvinylacetates and alcohols, as well as other polymeric materials including gum traganth, gum arabicum, alginates, e.g. alginic acid, and salts thereof, e.g. sodium alginates;

4.5. Inorganic thickening agents such as atapulgite, bentonite and silicates including hydrophilic silicon dioxide products, e.g. alkylated (for example methylated) silica gels, in particular colloidal silicon dioxide products as known and commercially available under the trade name Aerosil [c.f. Handbook of Pharmaceutical Excipients, loc. cit., p.p. 253-256] in particular the products Aerosil 130, 200, 300, 380, O, OX 50, TT 600, MOX 80, MOX 170, LK 84 and the methylated Aerosil R 972.

5 In the case of compositions in accordance with (A) which are intended for oral administration, such thickening agents may be included, e.g. to provide a sustained release effect. However, where oral administration is intended, the use of thickening agents as aforesaid will generally not be required and is generally less preferred. Use of thickening agents is, on the other hand, indicated, e.g. where topical application is foreseen.

10 Compositions in accordance with (A) above may also include one or more further ingredients in particular diluents, anti-oxidants [e.g. ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols, e.g. α -tocopherol (vitamin E)], flavouring agents and so forth. Use of an anti-oxidant, in particular a tocopherol, is particularly advantageous.

15 While it is foreseen, especially where oral administration is contemplated, that compositions in accordance with the invention as defined under (A) should comprise end dosage forms for administration as such, the present invention also provides pharmaceutical compositions comprising a cyclosporin as active ingredient and which are themselves oil-in-water microemulsions. Thus where oral administration is practiced, microemulsions obtained, e.g. by diluting a "microemulsion pre-concentrate" as defined under (A) with water or other aqueous medium may be employed as formulations for drinking. 20 Similarly, where topical application is foreseen, compositions comprising a hydrocolloid thickening agent, e.g. as set forth under (4.2.) or (4.4.) above will suitably also comprise water, thus providing an aqueous microemulsion in gel, paste, cream or like form. 25 Such compositions are also new. Accordingly in a yet further aspect the present invention provides:

30 B) A pharmaceutical composition comprising a cyclosporin as active ingredient (1) a hydrophilic phase, (2) a lipophilic phase, (3) a surfactant and water, which composition is an oil-in-water 35 microemulsion.

5 Compositions as defined under (B) may comprise any of components (1) to (3) as hereinbefore described in relation to compositions as defined under (A) and water. Compositions (B) are o/w microemulsions. Preferably they will exhibit stability characteristics as hereinbefore described in relation to microemulsions obtainable from compositions defined under (A).

10 Compositions in accordance with the present invention may be employed for administration in any appropriate manner, e.g. orally, e.g. in unit dosage form, for example in hard or soft gelatin encapsulated form, parenterally or topically e.g. for application to the skin, for example in the form of a cream, paste, lotion, gel, ointment, 15 poultice, cataplasm, plaster, dermal patch or the like, or for ophthalmic application, for example in the form of an eye-drop, -lotion or -gel formulation. Readily flowable forms, for example microemulsions, may also be employed e.g. for intralesional injection for the treatment of psoriasis, or may be administered rectally, e.g. 20 as an enema for the treatment of inflammatory bowel disease or Crohn's disease. Compositions in accordance with the invention are however primarily intended for oral or topical application, in particular application to the skin.

25 The relative proportion of ingredients in the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned, e.g. whether it is a "oil-in-water microemulsion pre-concentrate", or oil-in-water microemulsion. The relative proportions will also vary, depending on the particular function of ingredients in the composition, for example, in the case of a surfactant component of an "oil-in-water 30 microemulsion pre-concentrate", on whether this is employed as a surfactant only or both a surfactant and a co-solvent. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the product composition, e.g. in the case of a composition for topical use, 35

whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of the man skilled on the art. All indicated proportions and relative weight ranges described below are accordingly
5 to be understood as being indicative of preferred or individually inventive teachings only and not as not limiting the invention in its broadest aspect.

The amount of cyclosporin in compositions of the invention will of course vary, e.g. depending on the intended route of administration and to what extent other components, in particular components (2) to
10 (4) as hereinbefore described, are present. In general however the cyclosporin will be present in an amount within the range of from 0.05 especially 0.1 to 35% by weight based on the total weight of the
15 composition.

Components (1) will suitably be present in the compositions of the invention in an amount of from 0.5 to 90% by weight based on the total weight of the composition. In the case of compositions in accordance
20 with the invention comprising a component (1.1.) (e.g. Glycofurol or Transcutol), (1.1.) will generally be present in an amount of from 1 to 90% by weight, more commonly from 5 or 10 to 70% by weight based on the total weight of the composition. In the case of compositions in accordance with (A) or (B) above comprising a component (1.2.), (1.2.)
25 will generally be present in an amount of from 2 to 50% by weight based on the total weight of the composition. In the case of compositions in accordance with the invention comprising a component (2) or (3), these will each be generally present in an amount of from 0.5 to 90% by weight based on the total weight of the composition. In
30 an especially preferred aspect the present invention relates to:

- C) Compositions as defined under (A) above for oral administration, e.g. in a form suitable or convenient for oral administration.
- 35 For compositions as defined under (A) to (B) intended for non-topical administration and, in particular, for oral dosage forms (C):

- 5 a) The cyclosporin will generally be present in an amount of from 1 or 2 to 30%, suitably from 4 to 25% by weight based on the total weight of the composition. More suitably the cyclosporin will be present in an amount of from 5 to 25, especially to 20%, e.g. from 5 to 15% by weight based on the total weight of the composition;
- 10 b) Component (1.1) when present will generally be present in an amount of from 15 to 85, suitably from 20 to 80, more suitably from 25 to 70, e.g. from 30 to 50 or 60% by weight based on the total weight of the composition;
- 15 c) Cyclosporin and component (1.1.) when present will generally be present in a ratio of 1:0.75 to 20, suitably 1:1 to 15, more suitably 1:1 to 5, e.g. 1:1 or 1:1.5 to 4 p.p.w. [Cyclosporin: (1.1.)];
- 20 d) Component (1.2.) when present will generally be present in an amount of from 3 to 45, suitably 5 to 30% by weight based on the total weight of the composition;
- 25 e) Cyclosporin and component (1.2.) when present will generally be present in a ratio of 1:0.1 to 20, suitably 1:0.2 to 10 p.p.w.. More suitably they will be present in a ratio of 1:0.3 to 6, e.g. 1:0.5 to 3 p.p.w. [Cyclosporin: (1.1)].
- 30 f) Component (2) when present will generally be present in an amount up to 45%, suitably up to 40% by weight based on the total weight of the composition. More suitably component (2) will be present in an amount of from 2 to 45, yet more suitably from 3 to 35, most suitably from 5 or 10 to 30% by weight based on the total weight of the composition.
- 35 g) Components (2) and (1.1) when present will generally be present in a ratio of 1:0.5 to 40, suitably 1:0.5 to 20, more suitably 1:0.75 to 10, e.g. 1:0.75 to 4 p.p.w. [(2):(1)].

- h) Components (2) and (1.2) when present will suitably be present in a ratio of 1:0.075 to 22, suitably 1:0.1 to 15, most suitably 1:0.15 to 6 p.p.w., e.g. 1:0.5 to 3 p.p.w. [(2):(1.2)].
- 5 i) Components (3) when present [including both components of type (3.1.) and (3.2.)], will generally be present in an amount of up to 90, e.g. from 20 to 90% by weight based on the total weight of the composition. More suitably components (3) will be present in an amount of from 20 or 25 to 80 or 90% by weight based on the total weight of the composition, e.g. from 25 to 55% when a component (1.1) is employed or from 40 to 75% when a component (1.2) is employed.
- 10 j) Cyclosporin and component (3) [including both components of type (3.1.) and (3.2.)] when present will generally be present in a ratio of 1:0.5 to 20, more suitably to 12 p.p.w.. Appropriately they will be present in a ratio of 1:1 to 10 p.p.w., e.g. 1:1 to 5 p.p.w. when a component (1.1) is present or 1:3 to 8 p.p.w. when a component (1.2) is present. [Cyclosporin: (3)].
- 15
- 20

For compositions as defined under (A) and (B) ["oil-in-water microemulsion pre-concentrates" and oil-in-water microemulsions] the relative proportions of ingredients comprising (1) the hydrophilic phase, (2) the lipophilic phase and (3) the surfactant will vary with the concentration of cyclosporin present. They will also vary in relative proportion to each other.

25

Compositions according to (A) may thus be defined as comprising a cyclosporin together with (1) a hydrophilic phase [e.g. as defined under (1.1) or (1.2) above], (2) a lipophilic phase [e.g. as defined under (2.1) or (2.2) above] and a surfactant [e.g. as defined under (3.1) or (3.2) above], the relative proportions of cyclosporin: (1):(2):(3) being such that on contact with water, e.g. as hereinbefore indicated in relative proportions of 1:1 p.p.w. [cyclosporin+(1)+(2)+(3):H₂O] or more, an oil-in-water microemulsion

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is obtainable.

Similarly compositions according to (B) may be defined as comprising a cyclosporin together with components (1), (2) and (3) as aforesaid and water in relative proportions, e.g. as hereinbefore indicated, required to provide an oil-in-water microemulsion.

Compositions in accordance with (A) and (B) preferably comprise from 2 to 30, more preferably from 5 to 20, most preferably from 10 to 15% by weight of cyclosporin based on the total weight of cyclosporin plus components (1) + (2) + (3).

When (1) of compositions (A) or (B) is as defined under (1.1) above, e.g. comprises Transcutol or Glycofurol, components (1.1), (2) and (3) will preferably be present in amounts of from 15 to 85%, more preferably from 25 to 65% of (1.1), from 2 to 40, more preferably from 3 to 35 most preferably from 3 to 30% of (2) and from 15 to 85, more preferably from 25 to 55 or 60% of (3), all %ages being by weight based on the total of (1.1) + (2) + (3). Use of Glycofurol is of particular interest.

When (1) of compositions (A) or (B) is 1,2-propylene glycol [(1.2) above], components (1.2.), (2) and (3) will suitably be present in amounts of from 3 to 35%, more preferably from 3 to 25% of (1.2), from 2 to 35%, more preferably from 3 to 30% of (2) and from 45 to 90%, more preferably from 50 to 90%, e.g. from 55 to 80% of (3), all %ages being by weight based on the total of (1.2) + (2) + (3). As previously indicated, when (1) is 1,2-propylene glycol component (3) will generally comprise both a surfactant and a co-surfactant. When a co-surfactant is employed, surfactant and co-surfactant will suitably be present in a ratio of up to 50:1, preferably up to 20:1, more preferably up to 15:1, e.g. from 2 to 15:1 p.p.w. (surfactant: co-surfactant).

Fig. I attached, represents a three-way plot for relative concentrations of components (1.1) (e.g. Glycofurol), (2) (e.g.

Miglyol 812), and (3) (e.g. Cremophore RH40) in compositions according to (A) and comprising ca. 10% cyclosporin (e.g. Ciclosporin) by weight. Relative concentration of component (1.1) increases from 0% along the left hand margin of the plot to 100% at the lower right corner, as indicated by the arrow "1.1". Concentration of component (2) increases from 0% at the right hand margin of the plot to 100% at the lower left corner, as indicated by the arrow "2". Thus a composition comprising 50% of (1.1) and 50% of (2) only, is designated at the mid-point of the base-line of the plot. Relative concentration of component (3) increases from 0% at the base-line of the plot to 100% at the apex, as indicated by the arrow "3". Lines within the plot represent increments of 10%, from 0% at each margin to 100% at the apex opposite.

For compositions as defined under (A) and (B) the relative proportion of components (1.1), (2) and (3) will suitably lie within the area A defined by the line a of Fig. I. More suitably the relative proportion of components (1.1), (2) and (3) will lie within the area B defined by the line b of Fig. I, microemulsions based on these proportions being found to have greatest stability, e.g. of >24 hrs./an average particle size of less than 1,000 Å. Compositions in accordance with the invention comprising the components (1.1), (2) and (3) in relative proportion as defined above with reference to Fig. I accordingly represent especially preferred embodiments.

Fig. II attached, represents a three-way plot for relative concentrations of components (1.2), (2) e.g. Miglyol 812 and (3) in compositions according to (A) and comprising ca. 10% cyclosporin (e.g. Ciclosporin) by weight. In this case (3) comprises an appropriate surfactant/co-surfactant mixture, e.g. in a ratio of 11:1 p.p.w., for example comprising 11 p.p.w. Cremophor RH40 and 1 p.p.w. Glycerinmonooleate. Relative amounts of components (1.2), (2) and (3) are indicated, as for Fig. I, by arrows "1.2", "2" and "3" respectively.

For compositions as defined under (A) and (B) the relative proportions

of components (1.2), (2) and (3) will suitably lie within the area X defined by the line x of Fig. II. More suitably the relative proportion of components (1.2), (2) and (3) will lie within the area Y defined by line y of Fig. II. Most suitably the relative proportion of components (1.2), (2) and (3) will lie within the area Z of Fig. I defined by line z, microemulsions based on proportions within the areas Y and Z having an average particle size of the order of 1,100 Å and <200 Å respectively and a stability, e.g. of >24 hrs..

Compositions in accordance with (C) above may additionally include a thickening agent, though, as previously indicated, this will generally be less preferred. Suitable thickening agents include any of those hereinbefore described under (4) above. The amount of thickening agent present may vary e.g. depending on the required consistency of the end product, e.g. whether it is to be in a thickened flowable form, for example for filling into a capsule or the like, or sufficiently resilient to be mouldable or formable, e.g. for use in the manufacture of tablets or the like. The amount will of course also depend on the nature of the thickening agent chosen. In general components (4), when present will be present in an amount of up to 25% by weight based on the total weight of the composition, more suitably in an amount of up to 15 or 20% by weight, e.g. in an amount of from 0.5 or 5 up to 15 or 20% by weight based on the total weight of the composition.

Compositions in accordance with (C) may also include further additives or ingredients, e.g. as hereinbefore described with reference to compositions (A). In particular they may comprise antioxidants, e.g. in an amount of up to 0.5 or 1% by weight based on the total weight of the composition, and sweetening or flavouring agents, e.g. in an amount of up to 2.5 or 5% by weight based on the total weight of the composition.

Compositions (C) have been found to exhibit especially advantageous properties when administered orally, e.g. in terms of both the consistency and high level of bioavailability achieved. In particular, and in contrast with other galenic systems, e.g. as known from the

art, it has been found that such compositions are compatible with tenside materials, e.g. bile salts, present in the gastro-intestinal tract. That is, they are fully dispersible in aqueous systems comprising such natural tensides and are thus capable of providing microemulsion systems in situ which are stable and do not exhibit precipitation or other disruption of fine particulate structure. Function of such systems on oral administration remains independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual. Such compositions accordingly represent an especially preferred embodiment of the invention.

Compositions in accordance with (C) above will preferably be compounded in unit dosage form, e.g. by filling into orally administerable capsule shells, e.g. soft or hard gelatine capsule shells or by tabletting or other moulding process. Where compositions (C) are in unit dosage form, each unit dosage will suitably contain between 5 or 10 and 200mg cyclosporin, more suitably between 15 or 25 and 150mg, e.g. 25, 50 or 100mg cyclosporin. Thus unit dosage forms in accordance with the invention, suitable for administration 1x, 2x or 3x up to 5x daily (e.g. depending on the particular purpose of therapy, the phase of therapy etc...) will appropriately comprise e.g. 50mg or 100mg cyclosporin per unit dosage.

Compositions in accordance with (B) above for oral administration may be prepared, by addition of compositions as described in relation to (A) or (C) above to water or any other aqueous system, e.g. in relative proportions (composition:H₂O) as hereinbefore indicated, for example a sweetened or flavoured preparation for drinking. Such compositions may thus comprise any system as hereinabove defined or described in relation to compositions (A) or (C), plus sufficient water to form a microemulsion.

Compositions as defined under (D) above are, in particular, intended for oral administration, though use in form suitable, e.g. for topical, including dermal and topical ophthalmic, parenteral or rectal

administration, as well as for intralesional injection, is also embraced.

5 Compositions as defined under (A) and (B) are also of particular interest for topical administration. Accordingly in a yet further aspect the present invention provides:

10 D) Compositions as defined under (A) or (B) above for topical, especially for dermal application, i.e. in a form suitable or convenient for topical application.

15 Where topical administration is contemplated, the cyclosporin will suitably be present in an amount of from 0.05, more preferably from 0.1, to 15% by weight based on the total weight of the composition. More preferably the cyclosporin will be present in an amount of from 0.1 to 10% by weight.

20 In the case of compositions (D), the relative proportion of components (1), (2) and (3) will be as hereinbefore described for such compositions, e.g. with reference to Figs. I and II.

25 Compositions (D) will suitably comprise one or more carriers or diluents and/or other ingredients providing a carrier system, e.g. thickening agents, emulsifying agents, preserving agents, moisturising agents, colourants and so forth.

30 Compositions (D) may be in any form suitable for topical application, e.g. application to the skin surface, for example flowable, e.g. liquid or semi-liquid form, in the form of a powder or in the form of a topically applicable spray. Examples of suitable flowable forms include e.g. gels, including oil-in-water and water-in-oil emulsions or microemulsions, creams, pastes and ointments and the like as well as lotions, and tinctures, etc.. Such compositions also include, e.g. cataplasms and poultices as well as transdermal patch systems.

35 Selection of excipients for the preparation of such formulations will,

of course, be determined by the type of formulation desired as well as the particular condition to be treated, the status of the condition, area to be treated, skin condition and effect desired. Thus chronic psoriatic plaques will more suitably be treated with hydrophobic, e.g. fat-based compositions, for example compositions in accordance with the invention comprising a petrolatum based ointment or cream as carrier medium. In contrast, compositions for use in the treatment of disease conditions involving acute phase inflammatory processes will more appropriately be treated with more hydrophilic compositions, e.g. compositions in accordance with the invention in the form of an oil-in-water emulsion or gel. Although, compositions (D) may comprise, e.g. lower alkanols, for example ethanol, for example as diluent or diluent component, use of these will preferably be avoided, e.g. where compromised skin is to be treated, as in the case of psoriasis. Preferred compositions (D) are thus free or substantially alkanol free, e.g. contain less than 5%, more preferably less than 2%, e.g. from 0 to 1% by weight alkanolic components, in particular of ethanol.

Especially preferred compositions (D) are compositions in accordance with (A) or (B) additionally comprising: (5) a (further) pharmaceutically acceptable diluent or carrier which is non-miscible with component (1.1.). Compositions as aforesaid will preferably take the form of a water-free or substantially water-free emulsion, i.e. comprise less than 10%, preferably less than 5%, most preferably less than 1% water. Such emulsions include both emulsions comprising component (1.1.) in (5), and emulsions comprising (5) in (1.1.). Preferably they will comprise an emulsion of (1.1.) in (5).

Suitable components (5) include, for example:

- 5.1. Solid hydrocarbons, for example petroleum jellies, e.g. white petrolatum or Vaseline^R, ceresin and solid paraffins, as well as waxes including animal, vegetable and synthetic waxes such as, for example, spermaceti, carnauba and bees wax;

- 5.2. Liquid hydrocarbons, e.g. liquid paraffins and fatty acid esters such as isopropylmyristate and cetyl palmitate;
- 5.3. Non-volatile silicones including silicone oils and pastes, and silicone-polyalkyleneoxide co-polylymers [c.f. Fiedler, loc.cit., pp. 1109 and 1110] for example such as known and commercially available under the trade name Piroethicon.

Components (5) will suitably be present in compositions (D) in an amount of up to 80%, e.g. from 5 to 70%, preferably from 25 to 60% by weight based on the total weight of the composition.

By use of individual ingredients (5) or mixtures thereof, emulsions may be obtained in liquid or semi-solid form depending on, e.g., desired requirements for topical application.

Compositions (D) will suitably also comprise a surfactant. Suitable surfactants include, in particular, lipophilic surfactants, including any of those listed under (3.2.1.) to (3.2.7.) above, especially surfactants having an HLB of ca. 5-7. Examples of surfactants of particular utility in relation to compositions (D) include for example, surfactants as described under (3.1.2.), and (3.2.3.) above as well as glycerol monstearate, propyleneglycol monostearate, diethyleneglycol monostearate and glycerol ricinoleate.

Surfactants as aforesaid will suitably be present in compositions (D) in an amount of up to 60%, e.g. from 2 to 50%, preferably from 10 to 40% by weight based on the total weight of the composition.

Compositions (D) may further comprise one or more consistency promoting agents, for example microcrystalline waxes, vegetable oils such as olive oils, corn oils and kernel oils, and vegetable oil derivatives including hydrogenated vegetable oils and vegetable oil partial-glycerides, e.g. in an amount of from 0.1 to 10%, preferably

Compositions (D) will also suitably comprise:

- 5 - an anti-oxidant, e.g. any of the antioxidants hereinbefore described in relation to compositions (A), for example in an amount of from 0.01 to 0.5% by weight based on the total weight of the composition;
- 10 - an anti-bacterial agent, e.g. benzyl alcohol, methyl- or propyl-paraben, benzalkonium chloride, benzoic acid, sorbic acid or chlorobutanol, for example in an amount of from 0.05 to 2% by weight based on the total weight of the composition;
- 15 - a stabilizer such as microcrystalline starch, sodium EDTA or magnesium sulfate, e.g. in an amount of from 0.1 to 10% by weight based on the total weight of the composition; and/or
- 20 - a skin penetration enhancer, for example a C₁₂₋₂₄ mono- or poly-unsaturated fatty acid or alcohol (e.g. vaccenic, cis-vaccenic, linoleic, linolenic, elaidic oleic, petroselinic, erucic or nervonic acid or any of their corresponding alcohols, especially oleic acid or oleyl alcohol), or
- 25 1-dodecylazacycloheptan-2-one also known as Azone (c.f. Fiedler, loc. cit., p. 190), e.g. in an amount of from 1 to 20, suitably from 3 to 15% by weight based on the total weight of the composition.

30 In addition to the foregoing the present invention also provides a process for the production of a pharmaceutical composition as hereinbefore defined, e.g. as hereinbefore defined under anyone of (A) to (D) above, which process comprises bringing the individual components thereof into intimate admixture and, when required

35 compounding the obtained composition in unit dosage form, for example filling said composition into gelatin, e.g. soft or hard gelatin, capsules.

In a more particular embodiment the invention provides a process for the preparation of a composition as defined under (A) or (B) above, which process comprises bringing a cyclosporin, e.g. Ciclosporin, into intimate admixture with a component (1.1) or (1.2) as hereinbefore
5 defined and with a component (2) and a component (3) as hereinbefore defined, the relative proportions of component (1.1) or (1.2), (2) and (3) being chosen such that a composition as defined under (A) is obtained and further, when required, contacting said obtained composition (A) with water, so as to obtain a composition as defined
10 under (B) and when required, compounding an obtained composition (A) in unit dosage form, e.g. soft or hard gelatin capsule form.

In a specific embodiment the present invention provides a process for producing a composition as defined under (A) above, which process
15 comprises intimately admixing a cyclosporin, e.g. Ciclosporin, with a component (1.1) or (1.2) as hereinbefore defined, and a component (2) and a component (3) as hereinbefore defined, the relative proportion of the components (1.1) or (1.2), (2) and (3) being selected relative to the quantity of cyclosporin employed such that an "oil-in-water
20 microemulsion pre-concentrate", e.g. composition capable on addition to water, e.g. in a ratio of at least 1:1 p.p.w. (composition:H₂O) of providing a system comprising a dispersed or particle phase of which the individual particles have a size of less than 2,000 Å, preferably of from about 100 to about 1,000 Å is obtained.

The preferred cyclosporin in relation to the compositions of the invention is Ciclosporin. A further preferred cyclosporin to which the teachings of the present invention are applicable is
25 [Nva]²-Ciclosporin, also known as cyclosporin G.

The following examples are illustrative of compositions in accordance with the present invention. Examples 1 and 2 illustrate the preparation of compositions in oral unit dosage form, suitable for
30 use, e.g. in the prevention of transplant rejection or for the treatment of autoimmune disease, e.g. any of the autoimmune diseases or conditions hereinbefore described, on administration of from 1 to 5

unit dosages/day. Example 3 illustrates the preparation of compositions for topical application, suitable for treatment, e.g. of atopic or contact dermatitis, psoriasis or hair loss, on application at the desired site of therapy, e.g. dermatitidic reaction or psoriatic lesion or to the scalp, at regular intervals, e.g. once, twice or three times per day.

The examples are described with particular reference to Ciclosporin. However, equivalent compositions may be obtained employing any other appropriate cyclosporin. In particular equivalent compositions may in all cases be obtained on replacement of Ciclosporin with [Nva]²-Ciclosporin in the same amount as indicated for Ciclosporin.

EXAMPLE 1

Preparation of oral dosage forms: "oil-in-water microemulsion pre-concentrate" type:

5

1.1.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
	(1.1) Glycofurol 75	180.0
10	(2.1) Miglyol 812	90.0
	(3.1.1) Cremophor RH 40	<u>180.0</u>
	TOTAL	500.0

15

The cyclosporin is dissolved in (1.1) with stirring at room temperature and (2.1) and (3.1.1) are added to the obtained solution, again with stirring. The obtained mixture is filled into a size 1 hard gelatin capsule and sealed using Quali-Seal technique.

20

The following compositions may be prepared analogously for filling into size 1 or 2 hard gelatin capsules:

1.2.	COMPONENT	QUANTITY (mg/capsule)
25	Cyclosporin (e.g. Ciclosporin)	50.0
	(1.1) Glycofurol 75	180.0
	(2.1) Miglyol 812	78.0
	(3.1.1) Cremophor RH 40	<u>192.0</u>
	TOTAL	500.0

30

35

1.3.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
	(1.1) Glycofurol 75	200.0
	(2.1) Miglyol 812	60.0
5	(3.1.1) Nikkol HCO-40	120.0
	Ethanol*	19.0
	Ascorbylpalmitate**	1.0
	TOTAL	450.0

10 *Co-solvent (hydrophilic phase)
 **Antioxidant

1.4.	COMPONENT	QUANTITY (mg/capsule)
15	Cyclosporin (e.g. Ciclosporin)	50.0
	(1) Glycofurol 75	100.0
	(2.1) Miglyol 812	75.0
	(3.1.7) Lecithin	75.0
	TOTAL	300.0

1.5.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	100.0
	(1.1) Glycofurol 75	260.0
25	(1.2) Propyleneglycol	50.0
	(2.1) Myritol 318	100.0
	(3.1.1) Cremophor RH 40	340.0
	BHA*	5.0
	TOTAL	855.0

30 *Anti-oxidant

1.6.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
	(1.2) 1,2-Propyleneglycol	68.0
	(2.1) Miglyol 812	68.0
5	(3.1.1) Cremophor RH 40	250.0
	(3.2.5) Glycerol monooleate*	<u>24.0</u>
	TOTAL	460.0

10	1.7.	COMPONENT	QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	50.0
		(1.2) 1,2-Propyleneglycol	68.0
		(2.1) Miglyol 812	24.0
		(3.1.1) Cremophor RH 40	250.0
15		(3.2.5) Glycerol monooleate*	<u>68.0</u>
		TOTAL	460.0

20	1.8.	COMPONENT	QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	100 .0
		(1.2) 1,2-Propyleneglycol	75.0
		(2.1) Miglyol 812	25.0
		(3.1.1) Cremophor RH 40	150.0
		(3.2.5) Glycerol monooleate*	<u>150.0</u>
25		TOTAL	500.0

30	1.9.	COMPONENT	QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	50.0
		(1.2) 1,2-Propyleneglycol	200.0
		(2.1) Miglyol 812	50.0
		(3.1.1) Cremophor RH 40	150.0
		(3.2.7) Generol 122 E16*	<u>50.0</u>
35		TOTAL	500.0

1.10.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.2)	1,2-Propyleneglycol	75.0
(2.1)	Miglyol 812	75.0
(3.1.1)	Cremophor RH 40	250.0
(3.2.7)	Generol 122 E25*	50.0
	TOTAL	500.0
	*Co-surfactant	

Compositions 1.1, 1.2, 1.6 and 1.7 are especially preferred. Equivalent compositions to 1.1 to 1.5 can in all cases be prepared replacing the Glycofurol component with Transcutol in the same or equivalent amount.

Equivalent compositions to 1.1 to 1.5 may be prepared but replacing the 50mg amount of cyclosporin with 15, 20 or 100mg cyclosporin (e.g. Ciclosporin) the quantities of the remaining components for each composition remaining as indicated.

EXAMPLE 2

Preparation of oral dosage forms: thickened "oil-in-water microemulsion pre-concentrate" type:

2.1.	COMPONENT	QUANTITY (mg/capsule)
	Cyclosporin (e.g. Ciclosporin)	50.0
(1.1)	Glycofurol 75	180.0
(2.1)	Miglyol 812	90.0
(3.1.1)	Cremophor RH 40	180.0
(4.2)	Methocel K100	100.0
	TOTAL	600.0

Ciclosporin and (1.1) to (3.1.1) are combined as in example 1 and the obtained mixture mixed homogeneously with (4.2). The product is filled into size 2 hard gelatin capsules.

The following composition may be obtained analogously:

	2.2.	COMPONENT	QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	50.0
5		(1.1) Glycofurol 75	180.0
		(2.1) Miglyol 812	90.0
		(3.1.1) Cremophor RH 40	180.0
		(4.6) Aerosil 200	9.0
		(4.2) Methocel K100	<u>100.0</u>
10		TOTAL	609.0

	2.3.	COMPONENT	QUANTITY (mg/capsule)
		Cyclosporin (e.g. Ciclosporin)	100.0
		(1.1) Glycofurol	210.0
15		(2.1) Myritol 318	90.0
		(3.1.1) Nikkol HCO-60	170.0
		(4.2) Klucel EF	<u>30.0</u>
		TOTAL	600.0

20

Equivalent compositions to 2.1 to 2.3 can be prepared replacing the Glycofurol component with Transcutol in the same or equivalent amount.

25 EXAMPLE 3

Preparation of topically applicable form: "oil-in-water microemulsion pre-concentrate" type:

30	COMPONENT	% BY WEIGHT
	Cyclosporin (e.g. Ciclosporin)	0.1
	(1.1) Glycofurol	50.0
	(2.1) Miglyol 812	16.6
	(3.1.1) Cremophor RH 40	33.3

35 The above composition is prepared analogously to example 1. An

equivalent composition is obtained on replacement of the Glycofurol component with Transcutol. The composition may be made the basis of a cream, gel or the like by combination with further additives, e.g. hydrocolloid thickening agents, paraffins etc... as hereinbefore described.

Utility of compositions in accordance with the invention may be shown in animal or clinical trials, for example performed as follows:

BIOAVAILABILITY STUDY FOR COMPOSITIONS IN ACCORDANCE WITH THE INVENTION IN THE DOG

a) Test compositions

COMPOSITION I	as per example	1.1
COMPOSITION II	"	1.2
COMPOSITION III	"	1.6
COMPOSITION IV	"	2.1
COMPOSITION V	"	2.2

b) Test method

Groups of 8 beagle dogs (male, ca. 11-13kg) are used. Animals receive no food within 18 hours of administration of test composition but are allowed free access to water until administration. Test compositions are administered by gavage, followed by 20ml NaCl 0.9% solution. The animals are allowed free access to food and water three hours after administration of test composition.

2ml blood samples (or 5ml for the blank) are taken from the vena saphena and collected in 5ml plastic tubes containing EDTA at -15min. (blank), 30min., and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post administration. Blood samples are stored at -18°C pending assay.

Blood samples are analysed by RIA. Areas under the blood drug concentration versus time curves are calculated by the trapezoidal rule. Analysis of variance is performed with respect to AUC (area under curve), Cmax (maximum concentration) and Tmax (time of maximum).

c) Results

Calculated average AUC (in ng hr./ml⁻¹) and Cmax (in ng/ml⁻¹) values from typical trial runs are shown in the following table, together with calculated variation in response between test animals receiving the same composition (CV).

COMPOSITION	AUC (0-24h)	CV (%)	Cmax	CV%
I	2969	46.1	655	42.4
II	3315	35.9	606	29.0
III	3392	33.0	623	25.0
IV	4010	35.1	756	30.0
V	2769	27.8	469	21.7

As will be seen from the above table, compositions in accordance with the invention exhibit high bioavailability (AUC and Cmax.) coupled with relatively low variability in subject response both for AUC and Cmax.

Comparable advantageous results may be obtained employing other compositions in accordance with examples 1 and 2 herein, in particular the compositions of example 1.

The advantageous properties of the compositions of the invention on oral administration may also be demonstrated in clinical trials, e.g. performed as follows:

Trial subjects are adult volunteers, e.g. professionally educated males of from 30 to 55 years. Trial groups suitably comprise 12 subjects.

5 The following inclusion/exclusion criteria are applied:
Inclusion: Normal screening ECG; normal blood-pressure and heart rate; body weight = 50-95kg.
Exclusion: Clinically significant intercurrent medical condition which
10 might interfere with drug absorption, distribution, metabolism, excretion or safety; symptoms of a significant clinical illness in the two-week pre-trial period; clinically relevant abnormal laboratory values or electrocardiogram; need for concomitant medication during the entire course of the study; administration of any drug known to have a well-defined potential toxicity to a major organ system within
15 the previous 3 months; administration of any investigational drug within 6 weeks prior to entry into the trial; history of drug or alcohol abuse; loss of 500ml or more blood within the past 3 month period; adverse drug reaction or hypersensitivity; history of allergy requiring drug therapy; Hep.-B/HIV-positive.

20 Complete physical examination and ECG is performed pre- and post-trial. The following parameters are evaluated within 1-month periods pre- and post-trial:
Blood: - red blood cell count, haemoglobin, hematocrit, erythrocyte
25 sedimentation, white blood cell count, smear, platelet count and fasting glucose;
Serum/plasma - total protein and electrophoresis, cholesterol, triglycerides, Na⁺, K⁺, Fe⁺⁺, Ca⁺⁺, Cl⁻ creatinine, urea, uric acid, SGOT, SGPT, -GT, alkaline phosphatase, total bilirubin, α-amylase;
30 Urine - pH, microalbumin, glucose, erythrocytes, ketone bodies, sediment.
Creatinine clearance is also determined 1-month prior to trial entry.

Subjects each receive trial compositions in randomised sequence.
35 Compositions are administered orally, once to a total dose of 150mg cyclosporin, e.g. Ciclosporin, and at least 14 days are allowed

between each administration.

Administration is performed in the morning after an overnight fast of 10hrs. with only water allowed. Only caffeine-free beverages are permitted within the 24hr. period following administration. Subjects are not allowed to smoke within the 12hr. period following administration. Subjects receive a standardised lunch 4 hrs. following administration.

Blood samples (2ml) are taken 1 hr. prior to administration and post-administration at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 14, 24, 28 and 32 hrs.. For determination of creatinine 2ml blood samples are taken immediately prior to administration and at 12, 24 and 48 hrs. post-administration. Samples for cyclosporin determination are collected in two EDTA coated polystyrene tubes (1ml each) at each time point and are deep frozen at -20°C after gentle agitation. Cyclosporin is assayed in whole blood using RIA with specific and/or non-specific MAB assay - detection limit in both cases = ca. 10ng/ml.

In one such trial COMPOSITION I above in accordance with the invention (hard gelatin encapsulated form) is compared with COMPOSITION X.

COMPOSITION X [COMPARATIVE (ART) COMPOSITION]

Unit dosage form (soft gelatin capsule) comprising

Ciclosporin.....	50mg
Labrafil.....	150mg
Ethanol.....	50mg
Maize oil.....	<u>213mg</u>
Total	463mg/dosage.

(= current Sandimmun oral, drink solution)

In a trial performed in this manner a bioavailability level of 149.0% (± 48) is recorded for COMPOSITION I as compared with COMPOSITION X (for which bioavailability achieved is set as 100%). AUC values (0-32 hrs. ng.h/ml) and Cmax. values (ng/ml) established for COMPOSITION I are 2992 (± 627) and 882 (± 18) respectively as compared with 2137 (± 606) and 515 (± 180) for COMPOSITION X.

Figs. III and IV attached provide superimposed graphical representations from such a trial of whole blood Ciclosporin concentrations recorded for all 12 trial participants following single oral administrations of COMPOSITION I (Fig. III) and COMPOSITION X (Fig. IV), each in an amount providing a Ciclosporin dosage of 150mg, as determined by specific monoclonal RIA. Blood concentration (in ng/ml) is recorded vertically, and time (in hrs.) horizontally.

Comparison of Figs. III and IV clearly demonstrates the marked reduction in variability of inter-subject response with respect to bioavailability parameters recorded, on administration of COMPOSITION I as compared with COMPOSITION X. The determined coefficient of variation [(standard deviation/mean value) \times 100] with respect to Cmax. for COMPOSITION X is 35% as compared with a value of only 20% for COMPOSITION I.

Similar or equivalent results may be obtained following oral administration of other compositions in accordance with the invention, e.g. as herein described in the examples, in particular the compositions of example 1.

IN VIVO TESTING FOR TOPICAL FORMS

ALLERGIC CONTACT DERMATITIS TEST IN THE GUINEA PIG

Guinea pigs (Hartley, male, 400-500g) are sensitised by application of 50 μ l, 0.5% DNFB in acetone/olive oil (4:1) applied to marked areas on the shaven, left and right flank. This second challenge exposure

induces an allergic inflammation, leading to reddening and cellular infiltration (thickening) of the skin. Test composition (e.g. in accordance with example 3 above) in an amount of from 200-250mg is applied with a spatula to the DNFB treated area of the right flank. The left flank is similarly treated with placebo as control.

Application of test composition/placebo is effected 5x at intervals of 20 mins., 8 hrs., 24 hrs., 32 hrs., and 48 hrs., after the challenge. Skin thickness at the site of application is determined before each application, and again 8 hrs. after the last application, by raising the skin into a fold and measuring the thickness of this. Degree of reddening or inflammation is also estimated visually on a scale of from 0 to 4. Efficacy of test preparation in preventing inflammatory response is determined by comparison with results recorded for placebo treated flanks.

In the above test method substantial reduction in skin thickening as compared with placebo are achieved following first application of test composition, e.g. in accordance with example 3 continuing through treatment until completion of the experiment.

The following results are recorded for the composition of example 3

TIME AFTER CHALLENGE (HRS)	8	24	32	48	56
% INHIBITION OF SKIN THICKNESS / US PLACEBO CONTROL	56	68	76	75	73

CLAIMS

1. A pharmaceutical composition comprising
a cyclosporin as active ingredient,
5 1) a hydrophilic phase,
 2) a lipophilic phase, and
 3) a surfactant,

which composition is an "oil-in-water microemulsion
10 pre-concentrate".
2. A composition according to claim 1 wherein the hydrophilic phase
 (1) comprises
 1.1) a pharmaceutically acceptable C₁₋₅ alkyl or tetrahydrofurfuryl di
15 - or partial-ether of a mono - or poly-oxy-alkanediol comprising
 from 2 to 12 carbon atoms.
3. A composition according to claim 2 wherein
 1.1) is diethylene glycol monoethyl ether or tetrahydrofurfuryl alcohol
20 polyethylene glycol ether.
4. A composition according to claim 1 wherein the hydrophilic phase (1)
 comprises
 1.2) 1,2-propylene glycol.
25
5. A composition according to any one of claims 2 to 4 wherein the hydro-
 philic phase (1) comprises a C₁₋₅ alkanol as additional hydrophilic
 phase component.
- 30 6. A composition according to claim 5 wherein the C₁₋₅ alkanol is ethanol.
7. A composition according to claim 5 or 6 wherein the hydrophilic phase
 (1) comprises less than 50 % of weight of said C₁₋₅ alkanol.
- 35 8. A composition according to any one of claims 2 to 4 wherein the hydro-
 philic phase (1) is free of C₁₋₅ alkanol.

9. A composition according to any one of claims 1 to 7 wherein the lipophilic phase (2) comprises a fatty acid triglyceride.
- 5 10. A composition according to claim 9 wherein said fatty acid triglyceride is a caprylic-capric acid triglyceride.
- 10 11. A composition according to any one of claims 1 to 10 wherein the surfactant (3) comprises a polyoxyethylene glycolated natural or hydrogenated vegetable oil.
- 15 12. A composition according to any one of claims 4 to 10 wherein the surfactant (3) comprises a surfactant and a co-surfactant.
- 20 13. A composition according to claim 12 wherein the surfactant (3) comprises a polyoxyethylene glycolated natural or hydrogenated vegetable oil as surfactant and a monoglyceride as co-surfactant.
- 25 14. A composition according to any one of claims 1 to 13 comprising from 0.1 to 35 % by weight of cyclosporin based on the total weight of the composition.
- 30 15. A composition according to any one of claims 1 to 14 for oral administration.
- 35 16. A composition according to claim 15 comprising from 5 to 20 % by weight of cyclosporin.
17. A composition according to claim 16 comprising from 5 to 15 % by weight of cyclosporin.
18. A composition according to any one of claims 15 to 17 wherein the lipophilic phase (2) is present in an amount of from 2 to 45 % by weight based on the total weight of the composition.
19. A composition according to claim 18 wherein the amount is from 10 to 30%.

20. A composition according to any one of claims 15 to 19 wherein surfac-
tant (3) is present in an amount of from 20 to 90 % by weight based on
the total weight of the composition.
- 5 21. A composition according to any one of claims 15 to 20 wherein the
hydrophilic phase (1) comprises a component (1.1) as defined in claim 2
or 3.
- 10 22. A composition according to claim 2, wherein (1.1) is present in an
amount of from 15 to 85 % by weight based on the total weight of the
composition.
- 15 23. A composition according to claim 22 wherein the amount is from 30 to
50% by weight.
- 20 24. A composition according to any one of claims 21 to 23 wherein the lipo-
philic phase (2) and (1.1) are present in a ratio of 1 : 0.75 to
10 p.p.w.
- 25 25. A composition according to claim 24 wherein the ratio is 1 : 0.75 to
4 p.p.w.
26. A composition according to any one of claims 21 to 25 wherein surfac-
tant (3) is present in an amount of from 25 to 80 % by weight based on
the total weight of the composition.
27. A composition according to claim 26 wherein the amount is from 25 to
55%.
- 30 28. A composition according to any one of claims 15 to 20 wherein the
hydrophilic phase (1) comprises (1.2) 1,2-propylene glycol.
- 35 29. A composition according to claim 28 wherein (1.2) is present in an
amount of from 3 to 45 % by weight based on the total weight of the
composition.

30. A composition according to claim 29 wherein the amount is from 5 to 30%.
- 5 31. A composition according to any one of claims 28 to 30 wherein the cyclosporin and (1.2) are present in a ratio of 1 : 0.1 to 20 p.p.w.
32. A composition according to claim 31 wherein the ratio is 1 : 0.5 to 3 p.p.w.
- 10 33. A composition according to any one of claims 28 to 32 wherein the lipophilic phase (2) and (1.2) are present in a ratio of 1 : 0.15 to 6 p.p.w.
- 15 34. A composition according to claim 33 wherein the ratio is 1 : 0.5 to 3 p.p.w.
35. A composition according to any one of claims 28 to 34 wherein surfactant (3) is present in an amount of from 40 to 75 % by weight based in the total weight of the composition.
- 20 36. A composition according to any one of claims 28 to 35 wherein the cyclosporin and surfactant (3) are present in a ratio of 1 : 3 to 8 p.p.w.
- 25 37. A composition according to any one of claims 28 to 35 wherein the surfactant (3) comprises a surfactant and a co-surfactant as set forth in claim 12 or 13 and wherein said surfactant and co-surfactant are present in a ratio of from 2 to 15 : 1 p.p.w.
- 30 38. A composition according to claim 2 or 3 wherein the relative proportion of components (1.1) : (2) : (3) lies within the area (A) defined by line (a) of accompanying Fig. I.
- 35 39. A composition according to claim 38, wherein the relative proportion lies within the area (B) defined by line (b) of Fig. I.

40. A composition according to claim 4, wherein the relative proportion of components (1.2) : (2) : (3) lies within the area X defined by line x of accompanying Fig. II.
- 5 41. A composition according to claim 40, wherein the relative proportion lies within the area Y defined by line y of Fig. II.
42. A composition according to claim 41, wherein the relative proportion lies within the area Z defined by line z of Fig. II.
- 10 43. A composition according to any one of claims 1 to 42 for oral administration and in unit dosage form.
44. A composition according to claim 43 in soft or hard gelatin encapsulated form.
- 15 45. A composition according to claim 43 or 44 comprising from 5 to 200 mg cyclosporin/unit dosage.
- 20 46. A composition according to claim 45 comprising from 15 to 100 mg cyclosporin/unit dosage.
47. A composition according to claim 46 comprising from 20 to 100 mg cyclosporin/unit dosage.
- 25 48. A pharmaceutical composition comprising a cyclosporin as active ingredient, (1) a hydrophilic phase, (2) a lipophilic phase, (3) a surfactant and water, which composition is an oil-in-water micro-emulsion.
- 30 49. A composition according to claim 48 wherein components (1), (2) and/or (3) are as defined in any one of claims 2 to 12.
- 35 50. A composition according to any one of claims 1 to 13, 48 and 49 comprising from 0.05 to 15 % by weight cyclosporin based on the total weight

of the composition in a form suitable or convenient for topical application.

51. A composition according to claim 50 comprising from 0.1 to 10 % by weight cyclosporin.

52. A composition according to claim 50 or 51 in flowable form, in the form of a powder, in the form of a topically applicable spray or in the form of a cataplasm, poultice or transdermal patch.

53. A composition according to claim 52 in the form of a gel, cream, paste, ointment or tincture.

54. A composition according to any of claims 1 to 53, wherein the cyclosporin is Ciclosporin.

55. A composition according to any of claims 1 to 53, wherein the cyclosporin is [Nva]²-Ciclosporin.

56. A composition according to claim 1, substantially as hereinbefore described, in particular with reference to any one of examples 1.1 to 2.3.

57. A composition according to claim 50, substantially as hereinbefore described, in particular with reference to example 3.

Dated this 14th day of September, 1989.

BY: TOMKINS & CO.,
Applicants' Agents,

(Signed)

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FIG. 1

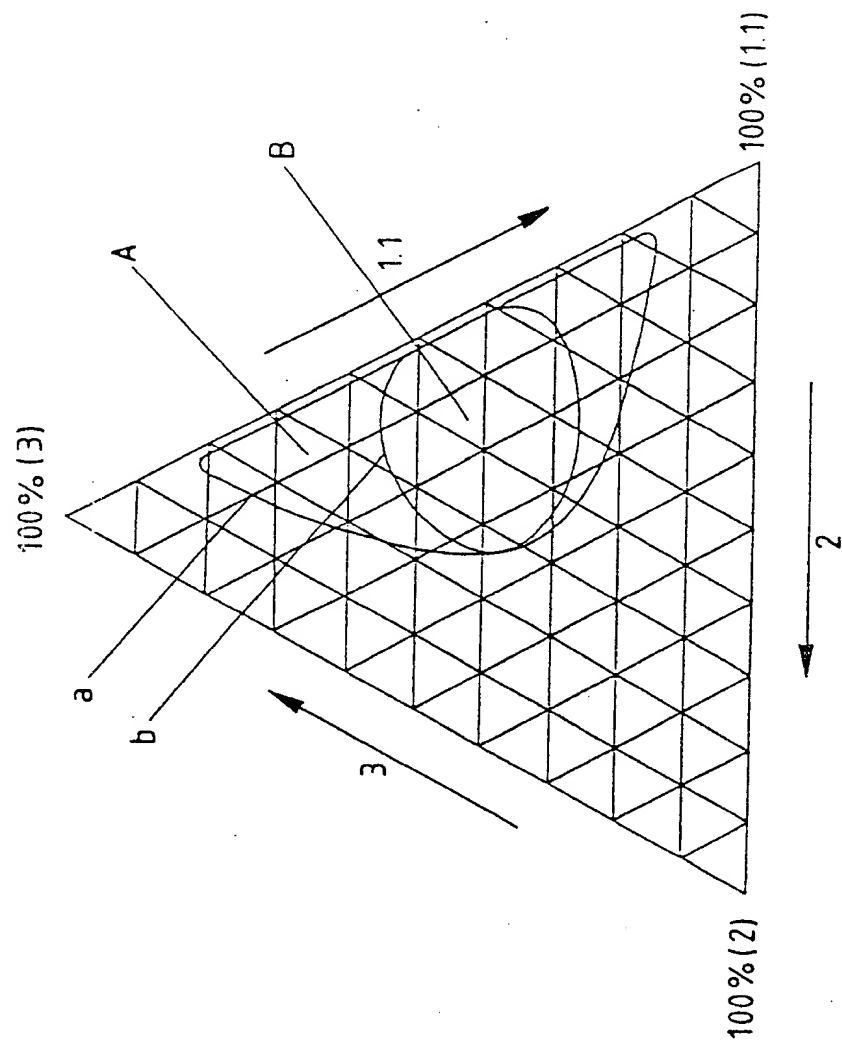


FIG. 2

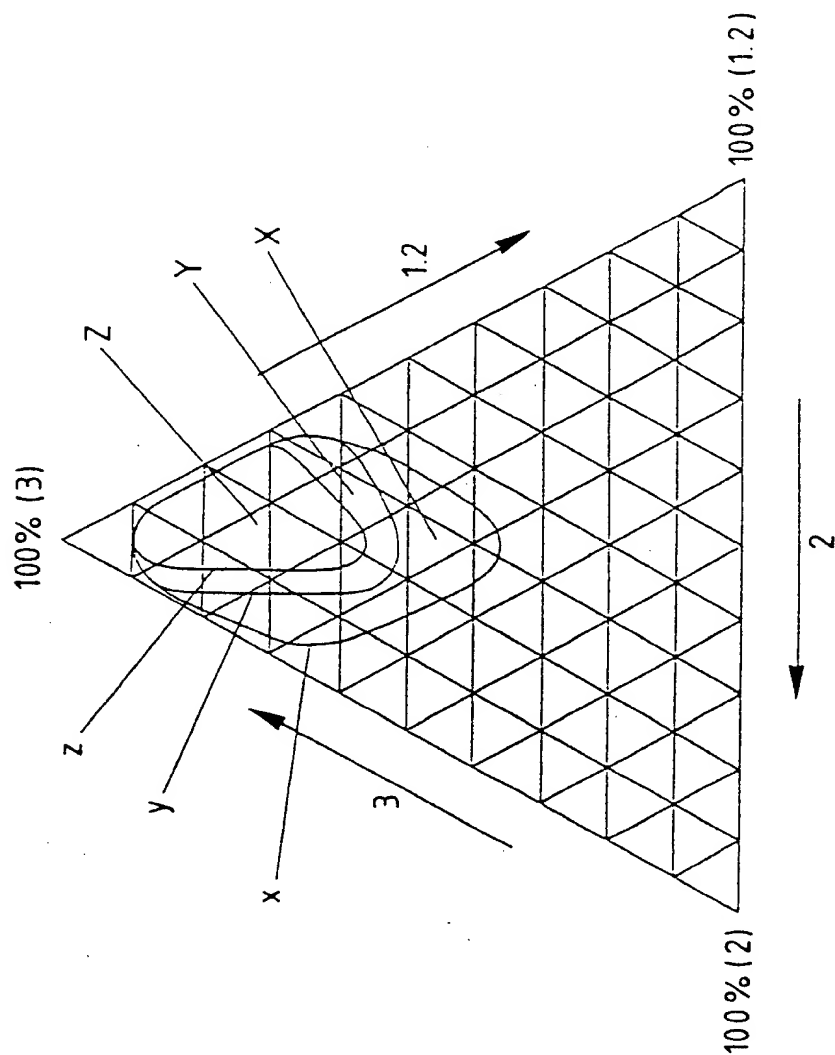


FIG. 3

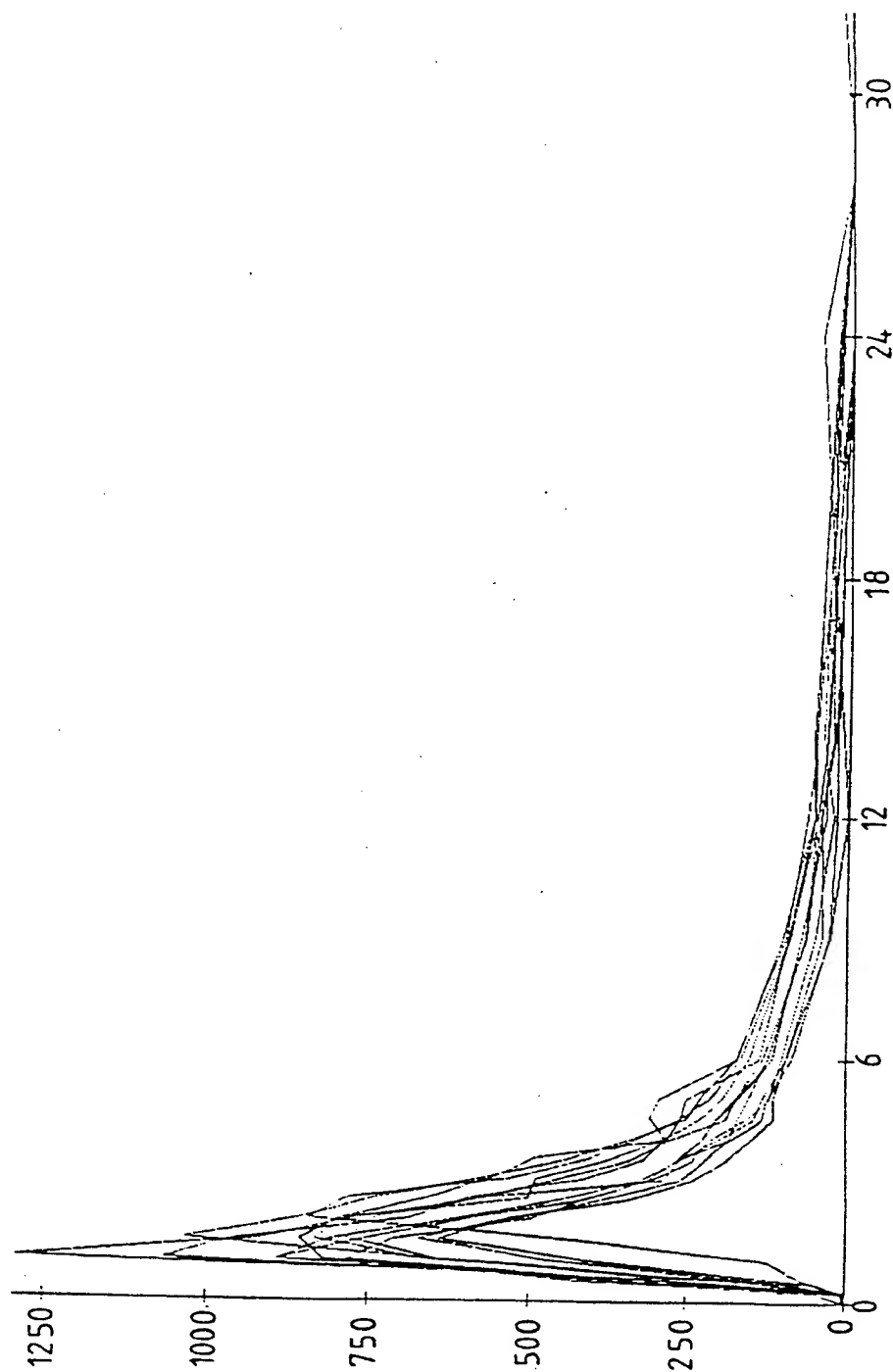


FIG. 4

